

Antipsychotic Drugs: From Receptor-binding Profiles to Metabolic Side Effects

Spyridon Sifias^a, Dimitrios Tzachanis^{a,b}, Myrto Samara^c and Georgios Papazisis^{a,*}

^aDepartment of Clinical Pharmacology, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece;

^bDepartment of Medicine, University of California San Diego, La Jolla, CA; ^c3rd Department of Psychiatry, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

Abstract: Background: Antipsychotic-induced metabolic side effects are major concerns in psychopharmacology and clinical psychiatry. Their pathogenetic mechanisms are still not elucidated.

Methods: Herein, we review the impact of neurotransmitters on metabolic regulation, providing insights into antipsychotic-induced metabolic side effects.

Results: Antipsychotic drugs seem to interfere with feeding behaviors and energy balance, processes that control metabolic regulation. Reward and energy balance centers in central nervous system constitute the central level of metabolic regulation. The peripheral level consists of skeletal muscles, the liver, the pancreas, the adipose tissue and neuroendocrine connections. Neurotransmitter receptors have crucial roles in metabolic regulation and they are also targets of antipsychotic drugs. Interaction of antipsychotics with neurotransmitters could have both protective and harmful effects on metabolism.

Conclusion: Emerging evidence suggests that antipsychotics have different liabilities to induce obesity, diabetes and dyslipidemia. However this diversity cannot be explained merely by drugs' pharmacodynamic profiles, highlighting the need for further research.

Keywords: Receptor-binding profiles, antipsychotics, metabolic side effects, neurotransmitters, obesity, diabetes, metabolic regulation, feeding behavior.

1. INTRODUCTION

Schizophrenia and most neuropsychiatric disorders have reciprocal connections with metabolic disturbances [1, 2]. Obesity, diabetes and metabolic syndrome are common comorbidities in patients with schizophrenia, especially on treatment with antipsychotics [3, 4]. They are more prominent in young, lean, female, drug-naïve patients and have been linked to health inequalities, polypharmacy, smoking, dietary habits, lack of exercise and illness characteristics [5]. Besides the direct connection between brain disorders and metabolic dysfunction, antipsychotic drugs can impair metabolic regulation *per se* [2]. Antipsychotics are strongly associated with the core components of metabolic syndrome (weight gain, glucose intolerance and dyslipidemia) and to a lesser degree with hypertension [4, 6], which if taken together can lead to therapy discontinuation, low self-esteem and cardiovascular disease [7].

Herein, we will review the current knowledge on central and peripheral mechanisms of antipsychotic-induced metabolic dysfunction (AIMD), based on drug binding profile.

1.1. Search Strategy

A literature search was conducted, using the Medline and Scopus electronic databases, including search terms and keywords for metabolic side effects (weight gain, obesity, food intake, diabetes, glucose intolerance, insulin resistance, insulin secretion, metabolic syndrome) combined with the keyword "antipsychotic" and search terms for the receptors (receptor, dopamine, serotonin, histamine, acetylcholine, muscarinic, epinephrine, norepinephrine, adrenergic). The search covered all peer-reviewed publications in English from January 2000 to December 2016. Additional papers were identified *via* citations in other reviewed papers. The binding profile of antipsychotic drugs was retrieved from PDSP and iPHACE databases along with relevant papers. Subsequently, papers that associate aspects of metabolic side effects with binding profiles were included.

2. METABOLIC REGULATION AND ANTIPSYCHOTIC-INDUCED METABOLIC DYSFUNCTIONS

2.1. Regulation of Energy Balance and Metabolism

Feeding behavior and metabolic regulation are closely and highly regulated systems. The metabolic system is regulated at two different levels involving the central and the peripheral system. The central nervous system regulates me-

*Address correspondence to this author at the Department of Clinical Pharmacology, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece; Tel/Fax: +30 2310 999323; E-mail: papazisg@auth.gr

metabolism through two different axes. The first axis originates mainly in hypothalamic centers. Satiety centers (e.g. POMC-melanocortin pathway) and hunger centers (e.g. NPY/AgRP pathway) are opposing in order to regulate energy balance. They have connections with higher-order brain regions, nuclei of the autonomous system and the reward system [8]. The second axis consists of the reward system that regulates food craving and pleasure of feeding. The ventral tegmental area, limbic cortex and striatum are core components of the reward system [9]. Feeding behavior, motivation and metabolism are regulated by direct and indirect connections between those axes [10]. The peripheral system consists of the gastrointestinal system, the liver, the pancreas, the adipose tissue (white and brown), the skeletal muscles, the immune system and the autonomous nervous system (ANS). The central and peripheral systems are closely interconnected *via* a wide array of neural and endocrine communications. Evolution biases metabolic homeostasis to an anabolic equilibrium point [11], a trend that can be potentiated by antipsychotic drugs.

2.2. Antipsychotic Drug Induced Metabolic Dysfunctions

Almost all antipsychotic drugs, typical and atypical, cause metabolic side effects [12] with quantitative and qualitative differences [13]. Meta-analyses and head-to-head comparisons of antipsychotic drugs have provided insights into the differential risk of weight gain induction and glucose and lipid handling disruption [4, 12, 14-18] (see 'risk' section in Table 1). Brexpiprazole and cariprazine are suggested to induce mild weight gain, but current experience with these drugs is limited [19, 20]. A recent meta-analysis classified antipsychotics based on their liability to cause metabolic syndrome according to the following order: clozapine > olanzapine ≥ quetiapine = risperidone = typical antipsychotics = amisulpride ≥ aripiprazole > placebo [6]. Despite this current evidence cannot elucidate the magnitude of the association between antipsychotics and diabetes/dyslipidemia [18].

The proposed model of AIMD suggests that antipsychotics disrupt metabolic regulation, by affecting both CNS and peripheral organs [21]. Regarding the CNS, they are suggested to activate hunger centers, inhibit satiety centers and disrupt food reward [22-24]. Additionally, they could impair locomotion and the flow of ANS to the periphery. These effects could mediate weight gain (increased energy intake, decreased energy expenditure) and alterations in peripheral metabolism [21, 23]. Weight gain impairs glucose and lipid metabolism and it is thought to be the core mechanism of AIMD.

In addition to that, *in vivo* and *in vitro* studies suggest that antipsychotic drugs could directly dysregulate peripheral metabolism. They may have direct effects on liver (increase lipogenesis, glucose output), adipose tissue (increase adipogenesis, lipogenesis and pro-inflammatory cytokines), skeletal muscles (decrease glucose uptake) [13, 25-27]. They can also derange pancreatic functions, disrupting insulin/glucagon secretion and repressing the compensation of pancreatic islets. These effects may mediate hyperglycemia,

diabetes and dyslipidemia [21, 28]. Antipsychotics could increase prolactin and ghrelin, hormones associated with metabolic dysfunctions. They can possibly alter the function of glucagon-like peptide-1 (GLP-1) along with the adipokines, leptin and adiponectin, which have beneficial effects on metabolism [13]. Antipsychotic-induced weight gain increases leptin levels in patients, which may be serving as negative feedback signal [29]. However, *in vivo* studies suggest that antipsychotics could induce leptin resistance by acting on satiety and reward centers [30, 31].

2.3. Translational Validity Issues of Animal Models of Antipsychotic-induced Metabolic Side Effects

Discrepancy of AIMD preclinical models is a major issue of translational neuropharmacology. Gender-dependent differences in antipsychotic-induced weight gain are evident in both clinical and preclinical setting. Clinical evidence, yet limited, suggest that women may be in higher risk of antipsychotic-induced weight gain than men [32]. However, female rodents seem to be more vulnerable to weight gain, especially olanzapine-induced [33]. This gender gap seems to be more prominent in chronic rather than acute antipsychotic administration [34].

Antipsychotic-induced hyperprolactinemia is more common in rodents than humans, but its contribution to weight gain may be limited [35]. However, prolactin seems to preferentially increase food intake in female rodents. Additionally, hyperprolactinemia is often accompanied by estradiol reduction in females, which could further increase food intake, and decreased testosterone in males, which could decrease lean body mass [36]. Histaminergic, dopaminergic and serotonergic signaling display also gender-dimorphism in rodents [32, 37]. Strain- and gender-dependent behavioral and pharmacokinetic differences could also play important roles. For example, male rats may be more susceptible to stress-induced decreased food intake, whereas females may be exposed to longer drug half-life [34, 38].

Rodent models of clozapine-induced weight gain display also inconsistent results regardless gender. In many models, clozapine may not affect or even decrease weight, partially explained by its sedative effects [34]. Despite the positive association of clozapine administration and weight gain in humans, clozapine may also induce weight loss to some individuals, possibly underpinning genetic factors or variable therapeutic response [39].

As a result, weight cannot solely provide high predictive validity of AIMD animal models. Adjusting experimental designs, such as routes of administration (antipsychotic drugs mixed with chow) and type of diet (high carbohydrate/fat), could diminish gender dimorphism and induce weight gain in olanzapine-treated male rodents [34]. Additionally, both clozapine and olanzapine can increase adiposity measures in rodents, irrespective of gender and weight gain [35, 40]. Examining parameters, such as body composition (fat and lean mass) and impaired satiation, along with carefully selected experimental designs and monitoring of sedation and extrapyramidal symptoms, could enhance the predictive validity of rodent models [34, 36, 41]. On the

Table 1. Receptor-binding profile and metabolic risk of antipsychotic drugs.

	RECEPTOR BINDING PROFILE																				RISK			
	D ₁	D ₂	D ₃	D ₄	H ₁	H ₂	H ₃	5-HT _{1A}	5-HT _{1B}	5-HT _{2A}	5-HT _{2B}	5-HT _{2C}	5-HT ₆	5-HT ₇	M ₁	M ₃	α ₁	α _{2A}	α _{2B}	α _{2C}	Transporter	Weight Gain	Glucose Abn	Lipid Abn
Olanzapine	++	++	++	++	+++	++	+		+	+++	++	++	+++	++	++	++	+	++	++	++		++++	++	++
Zotepine	++	+++	+++	+	+++	+		+	++	+++		+++	+++	++	+	+	+++	+	+++	++	SERT, NET	+++/+	(LD)	(LD)
Clozapine	+	+	+	++	+++	+		+	+	++	+++	++	++	++	+++	++	+++	++	++	++		+++/+	++	++
Chlorpromazine	++	+++	+++	+++	+++	+	+			+++	+++	++	+++	+++	++	++	+++	+	++	++		+++/+	+/+	+/+
Sertindole		+++	+++	+++	+			+	++	++++		+++		++			+++	+	+	+		+++/+	+/+	+/+
Iloperidone	+	+++	+++	++	+			++	++	+++		++	+	+			+++	+	+	++		+++/+	+/+	+/+
Risperidone	+	+++	+++	+++	+++	+		+	++	++++	++	++		+++			+++	++	++	+++		+++	+/+	+/+
(Nor)quetiapine	+	+	+		+++			++		++		+	+	++	+	+	++	+	+	++	NET	+++	+/+	++
Paliperidone	+	+++	+++	+++	++	+		+	++	+++		++	+	+++			+++	+++	+++	+++		+++	+/+	+/+
Asenapine	+++	+++	++++	+++	+++	+++		+++	+++	++++	++++	++++	++++	++++			+++	+++	++++	+++		++	+	+
Amisulpride		+++	+++	+++							++			++								++	+	++(LD)
Aripiprazole		+++	+++	+	++			+++	+	++	++++	++	+	++			++	++	++	++	SERT	++	+	+
Brexpiprazole	+	++++	+++	+++	++			++++	++	++++	+++	+	++	+++			+++	++	++	++++	SERT, NET	+(LD)	+(LD)	+(LD)
Cariprazine		++++	++++		++			+++		++	++++	+		+			+					+(LD)	+(LD)	+(LD)
Haloperidol	+	+++	+++	+++		+			+	+				+			++	+	+	+		+	+	+
Lurasidone	+	+++						+++		+++		+		++++			++	++		+++		+	+	+
Ziprasidone	+	+++	+++	++	++			+++	+++	++++	++	++++	++	+++			++	+	++	++	SERT, NET	+	+	+

A. Receptor-binding profile. Antagonism and inverse agonism are indicated by blue color whereas partial agonism by yellow. The number of crosses and color intensity are correlated to binding affinity. Quetiapine is demonstrated along with norquetiapine, a metabolite of the drug with distinct binding profile. $100 < K_i < 1000$: + weak association. $10 < K_i < 100$: ++ moderate association. $1 < K_i < 10$: +++ strong association. $1 > K_i$: ++++ very strong association. [Data taken from [30, 43-45, 48-50], PDSP [47] and iPHACE [46] databases]. **B. Metabolic risk.** The number of crosses are correlated to risk of weight gain (maximum ++++), glucose and lipid abnormalities (maximum ++). (LD): Limited Data, abn: abnormalities. [Data taken from [4, 12, 14-20].

contrary, preclinical models of antipsychotic-induced glucose dysregulation seem to be translational valid [42].

3. RECEPTOR MECHANISMS OF ANTIPSYCHOTIC-INDUCED METABOLIC SIDE EFFECTS

Antipsychotic drugs bind to a variety of neurotransmitter receptors [30, 43-50] (see ‘binding affinities’ in Table 1). Clinical and preclinical studies propose that H_1 , 5-HT_{2A} , 5-HT_{2C} , 5-HT_6 , D_2 , α_1 and M_3 are the key mediators of metabolic side effects [5, 30, 51-54]. Current research in the pathogenesis of AIMD focuses mainly on the central mechanism but recent advances in peripheral neurotransmitter receptors bring new insights [21].

3.1. Dopamine Receptors

Dopamine receptors are G protein-coupled receptors classified into D_1 -like (D_1 , D_5) that increase cAMP (G_{α_s}) and D_2 -like (D_2 , D_3 , D_4) that decrease cAMP (G_{α_i}). All antipsychotic drugs bind to D_2 receptors and altered dopaminergic signaling could be a ubiquitous contributor to AIMD (see Table 1). Proper dopaminergic neurotransmission in hypothalamus and reward system regulates feeding behaviors. Palatable food has rewarding properties and it could increase dopaminergic output in regions of the reward system. Presynaptic D_2 in midbrain inhibits dopamine release. Mice lacking D_2 autoreceptors display disinhibition of dopamine release in the striatum, accompanied by elevated reward-sensitivity and food-seeking behavior [55]. Reward system seems to adapt to chronic overconsumption of palatable food by decreasing striatal D_2 signaling. This reward-hyposensitive state could also trigger compensatory and compulsive food intake [9, 56]. Prior to initiation with amisulpride treatment, reduced reward-related activation of the dorsal striatum seems to predispose to weight gain in drug-naïve patients. However, amisulpride, and possibly other antipsychotics, seem to enhance the activation of striatal regions, which may also be related to weight gain [24]. As a result, D_2 antagonism could induce overeating, by both promoting reward-sensitive and reward-deficient states. In addition to food reward, striatal dopaminergic signaling seems to interact with insulin signaling and it could also affect glucose tolerance. According to that, dopamine depletion and decreased $D_{2/3}$ signaling in ventral striatum may be correlated to insulin resistance in healthy individuals [57].

Prefrontal cortex-amygdala network may also play important roles in regulating feeding. Prefrontal D_1 -expressing neurons may stimulate feeding by activating downstream nuclei of amygdala in mice [58], whereas $D_{2/3}$ stimulation in amygdala may reduce food intake in rats [59]. Hypothalamic dopaminergic neurotransmission regulates energy balance, glucose homeostasis, circadian rhythms and prolactin secretion [60]. Preclinical research suggests that hypothalamic D_1 signaling has site-dependent effects on feeding, whereas D_2 could act as satiety signal and inhibit food intake [61]. Rodent studies suggest also that D_2 mediates anorexic and hypophagic effects, such as by GLP-1 and leptin [31, 59]. Additionally, intracerebroventricular administration of D_2 antagonist to mice could induce hyperglycemia, accompanied by the activation of hypothalamic AMPK, which is cor-

related to AIMD [62]. Furthermore, D_2 antagonism in posterior pituitary and adipocytes elevates prolactin secretion [63]. Hyperprolactinemia has been accused for weight gain and insulin resistance. Risperidone, paliperidone, lurasidone, ziprasidone, amisulpride and sertindole increase significantly prolactin levels, however they do not have the same metabolic liabilities [17].

Despite conflicting results, D_1 agonism tends to increase food intake, but $D_{2/3}$ agonism may attenuate it [37, 64, 65]. Consequently, administration of D_2 antagonists, haloperidol or sulpiride, seems to be correlated to increased food intake and weight gain in rodents [34], whereas amisulpride could also reduce weight loss in a mouse model of anorexia nervosa [66]. Other preclinical studies demonstrated negligible effects on food intake and weight by administration of aripiprazole or haloperidol in rodents [34, 67], but haloperidol could potentiate weight gain induced by 5-HT_{2C} antagonists in rats [5, 68]. Additionally, administration of D_1 or D_2 agonists could alleviate clozapine-induced food intake in mice [69]. Accordingly, clinical and preclinical research suggests the beneficial effects of bromocriptine, a $D_{2/3}$ agonist, on weight and glycemic regulation in obesity or type 2 diabetes [60]. As a result, D_2 antagonism seems to be a supportive, rather than a core mechanism, of inducing AIMD.

Antipsychotic drugs can alter basal and stimulus-activated neurotransmitter secretion [42, 70]. Administration of haloperidol to male rats tends to attenuate palatable food-induced dopamine release in nucleus accumbens and food-induced eating, whereas long-term effects on prefrontal cortex seem to be negligible [71]. Conversely, atypical antipsychotics seem to preferentially increase dopaminergic output in prefrontal cortex compared to striatal regions, by acting on 5-HT_{1A} , 5-HT_{2A} and other receptors [72]. Antipsychotics with D_1 antagonist properties, such as olanzapine, could partially compensate increased cortical dopaminergic efflux. Clozapine, in comparison with other atypical antipsychotics, may act as D_1 partial agonist in prefrontal cortex [73]. Regarding that prefrontal D_1 may promote food intake, the different dopaminergic output of atypical antipsychotics could contribute to higher metabolic liabilities.

Dysfunction of the peripheral dopamine system seems to be associated with metabolic disturbances and altered glucose regulation. Human and rodent beta cells seem to express $D_{2/3}$ receptors, which may inhibit glucose-dependent insulin release and regulate proliferation of beta cells [63, 74]. Accordingly, *in vitro* administration of haloperidol or sulpiride to human islets seems to increase glucose-dependent insulin secretion [75], which could contribute to nutrient deposition and weight gain [51]. Subsequently, *in vivo* rodent studies suggest that chronic disinhibition of insulin secretion by D_2 antagonism could deplete insulin stores, disrupt pancreatic compensation and finally induce glucose intolerance [76-78].

3.2. 5-Hydroxytryptamine Receptors

The seven 5-HT receptor families are 5-HT_1 , 5-HT_5 (G_{α_i}), 5-HT_2 , 5-HT_4 , 5-HT_6 , 5-HT_7 ($G_{\alpha_{s/q}}$) and 5-HT_3 , a ligand-gated ion channel with excitatory properties. Central serotonin produces anorexigenic behaviors, modulates pe-

ripheral metabolism and circadian rhythms [79]. Satiety centers express 5-HT_{2C}, whereas hunger centers 5-HT_{1B} and 5-HT₆ [10]. Antagonism of 5-HT_{1B} and/or 5-HT_{2C} receptors by many antipsychotic drugs could switch the energy balance setpoint to a more anabolic state, inducing hunger and increasing food intake. *In vivo* rodent studies suggest that ventral tegmental 5-HT_{2c} stimulation inhibits binge eating by increasing dopaminergic signaling [80], but 5-HT_{1B} and 5-HT_{2B} may also be important [81]. Accordingly, administration of 5-HT_{2C} antagonist in rats induces weight gain, an effect that is potentiated by D₂ antagonist, haloperidol, which has no effect on weight alone [5, 68]. In addition, a pharmacodynamic-pharmacoepidemiological study proposes the association of 5-HT_{2C} antagonism and antipsychotic-induced diabetes, a relation that is potentiated by simultaneously H₁ antagonism [54]. 5-HT_{2A} antagonism is also associated with AIMD [53, 54]. Binding affinity to neocortical 5-HT_{2A} predicts quetiapine-induced weight gain in drug-naïve patients [82], but the receptor may also have important actions in the periphery. Conversely, antipsychotics with lower risk of weight gain, like ziprasidone, tend to be 5-HT_{1B} partial agonists. Administration of ziprasidone in rats, despite of having dual 5-HT_{2C} and D₂ antagonistic effects, increases energy expenditure and induces weight loss [83]. Concerning 5-HT₆, a pharmacodynamic analysis of clinical trials suggests that 5-HT₆ antagonism may be correlated to antipsychotic-induced weight gain [53].

Antipsychotic drugs can also have indirect effects on serotonin receptors by altering serotonergic efflux in different brain regions. Serotonergic efflux in cortical and subcortical regions seems to remain unchanged (e.g. lurasidone, ziprasidone) or even decrease (e.g. haloperidol, aripiprazole, olanzapine, clozapine). However, risperidone, and to a lesser extent quetiapine, may be the only exceptions. Risperidone could disinhibit serotonin neurotransmission, by 5-HT_{1A} and 5-HT_{2A} antagonism, resulting in increased serotonergic efflux [42, 70]. Additionally, long-term administration of haloperidol to rats seems to attenuate food-related increase of serotonin release in nucleus accumbens [71]. The supplementary and indirectly inhibition of serotonin receptors could further dampen serotonergic regulation of metabolic homeostasis and contribute to AIMD.

Serotonin may have multiple effects on beta islets, which seems to express 5-HT₁, 5-HT₂ and SERT. *In vitro* studies suggest that intracellular serotonin increases glucose-dependent insulin secretion whereas extracellular serotonin suppresses it [84]. Extracellular and intracellular serotonin levels can be modulated by serotonin transporters. Clinical data and *in vitro* studies propose that serotonin transporter inhibitors decrease insulin secretion and could accelerate the progression of diabetes [85, 86], possibly by increasing extracellular serotonin, but other mechanisms cannot be excluded [87]. 5-HT_{2C} antagonism seems to increase directly glucose-dependent insulin secretion in a mouse model of type 2 diabetes, but not in healthy mice [88]. However, 5-HT_{2C} transcripts have not been detected in human islets [89]. *In vitro* studies of human and rodent islets propose that 5-HT_{2A/B} stimulation increases glucose-dependent insulin secretion, in contrast to 5-HT_{1A/D} stimulation [89, 90]. Additionally, pancreatic 5-HT_{2B} may also promote proliferation

and adaption of beta islets during metabolic stress conditions [89]. Administration of 5-HT_{2A} antagonists to rodents suggests that they might directly decrease insulin secretion [52, 62, 77]. Central and peripheral administration of 5-HT_{1A} agonist to rodents suppresses insulin secretion, whereas 5-HT_{1A} antagonism seems to have no effect [52]. However, other 5-HT₁ subtypes may be more important in humans. In islets from healthy donors, extracellular serotonin inhibits insulin secretion, probably by 5-HT_{1D} stimulation. This effect is reversed on islets from T2D donors, which display compensatory increased expression of both 5-HT_{2A} and 5-HT_{1D} [90]. A recent study suggests that treatment initiation with aripiprazole or ziprasidone carries risk for diabetes in young antipsychotic-naïve patients, despite their estimated lower risk in other groups [91]. These drugs are potent 5-HT_{1D} agonists, which possibly explain this phenomenon in young patients.

3.3. Histamine Receptors

The families of histamine receptors are H₁ (G_{αq}), H₂ (G_{αs}) and the inhibitory H₃, H₄ (G_{αi}). CNS histamine is thought to be mainly anorexic reducing hunger and promoting satiety [92]. H₁ is expressed in satiety centers and their projections, whereas H₃ inhibits hunger centers and neurotransmitter release by acting as an autoreceptor [93]. Binding affinity to H₁ is correlated to antipsychotic-induced weight gain and diabetes [53, 54, 94]. Administration of olanzapine or risperidone to rats seems to increase food intake and reduce locomotor activity, accompanied by increased hypothalamic H₁R and activated AMPK [23, 95]. The above effects of olanzapine can be reversed by co-administration of H₁ agonist [95-97]. Additionally, central administration of H₁ antagonists activates hypothalamic AMPK and induces hyperglycemia in mice [62]. Conversely, H₁ antagonist could not increase weight in rats, questioning its role in antipsychotic-induced weight gain [68]. H₃ signaling may also contribute to AIMD, but its exact role is still not elucidated [98]. Regarding the crosstalk among hypothalamus-brainstem-periphery and the diverge actions of histamine [92, 99], antipsychotic-H₁ antagonism may have complex and supplementary contributions to AIMD.

There is evidence, yet controversial [28], that antipsychotic drugs could directly alter hepatic metabolism. A recent *in vivo* study suggests that olanzapine-induced dyslipidemia is accompanied with reduced activation of hepatic AMPK and increased hepatic H₁R expression in rats. Beta-histidine was able to reverse these actions, probably by acting on hepatic H₁ receptors [100]. Administration of clozapine to mice could increase fructose, but not glucose, absorption contributing to weight gain. Probably intestinal H₁ interacts with GLUT₅ function regulating fructose absorption. This interaction could contribute to weight gain and hepatic insulin resistance induced by antipsychotics [101, 102]. Other possible actions of peripheral histamine should also be noted. A study with healthy volunteers suggests that H_{1/2} may mediate indirectly glucose uptake by skeletal muscles after exercise and insulin sensitivity [103]. Interestingly, HR1 knockout mice are obese with increased atherosclerosis, whereas HR2 knockout mice display hyperlipidemia, hepatosteatosis but not atherosclerosis [104, 105]. Despite of

translational issues, H_1 antagonism could be an additive link between metabolic disturbances and cardiovascular risk.

3.4. Acetylcholine Receptors

Acetylcholine receptors are divided into muscarinic and nicotinic. Muscarinic receptors are GPCRs classified into M_1 , M_3 , M_5 (G_{α_q}) and M_2 , M_4 (G_{α_i}) [106]. Clozapine and olanzapine act as partial agonists/allosteric modulators of muscarinic receptors, whereas quetiapine, chlorpromazine and zotepine act as antagonists [43, 49]. Binding affinity to M_3 may be associated with antipsychotic-induced weight gain and diabetes [53, 54, 107]. Administration of olanzapine to rats increases M_3 density in both hypothalamus and DVC, possibly by M_3 antagonism. Increased M_3 density was associated with increased food intake and decreased insulin secretion [108]. However, central administration of M_1 antagonist to mice could not alter glucose metabolism [62]. Additionally, studies of olanzapine-treated rats suggest that presynaptic M_2 antagonism could reduce M_2 density in DVC, which may also contribute to increased food intake [109].

Pancreatic- M_3 deficient mice are prone to glucose intolerance whereas whole body- M_3 deficient mice are lean with a good metabolic profile suggesting complex roles of muscarinic signaling [110]. *In vitro* experiments with rat pancreatic islets suggest that M_1 and M_3 stimulation promotes basal and glucose-dependent insulin secretion respectively [111]. Accordingly, administration of M_3 antagonist to rats acutely inhibits glucose-dependent insulin secretion [77]. Clozapine and olanzapine as muscarinic partial agonists could both increase and decrease insulin secretion. This quite unique dual effect is consistent with *in vitro* and *in vivo* studies [28, 112, 113].

Other possible mechanisms cannot be excluded. During the cephalic phase of digestion, clozapine/olanzapine could antagonize acetylcholine at M_3 and decrease insulin secretion. The insufficient insulin levels during the cephalic phase increase post-prandial glucose blood levels, stimulating post-prandial insulin secretion. However, clinical evidence suggests that olanzapine increases both cephalic and post-prandial insulin levels, indicating complex and compensatory interactions of central and peripheral muscarinic signaling [51, 114]. Additionally, translational issues between human and rodent models should be furthered clarified. In contrast to rodents, human beta cells seem to express M_3 and M_5 , which increase insulin secretion, whereas delta cells express M_1 , which stimulates somatostatin secretion, a paracrine hormone that inhibits insulin secretion [115]. As a result, M_3 antagonism could decrease whereas M_1 antagonism indirectly increases insulin secretion in humans.

3.5. Adrenergic Receptors

Adrenergic receptors are classified into α_1 (α_{1A} , α_{1B} , α_{1D}), α_2 (α_{2A} , α_{2B} , α_{2C}) and beta (β_1 , β_2 , β_3). AIMD-related antipsychotics are potent inhibitors of α_1 receptors and less or equal of α_{2A} , whereas antipsychotics with lower metabolic risk tend to have equal affinities to α_1/α_{2A} (Table 1). Phenylpiperazines, such as aripiprazole, are also beta receptors (β_1 , β_2) antagonists [116].

In vivo rodent studies suggest that hypothalamic adrenergic receptors regulate energy balance, with α_1 and α_2 having opposing roles. Noradrenergic transmission to hypothalamus may mediate peripheral anorexic signals [117]. Central α_1 agonism seems to decrease food intake and weight gain whereas α_2 agonism has the opposite effects [30]. Additionally, central administration of α_1 antagonist to mice was able to induce hyperglycemia and activation of hypothalamic AMPK [62]. α_{2A} inverse agonism, in contrast to α_1 or α_{2B} antagonism, potentiates weight loss by norepinephrine transporter/serotonin transporter inhibitors in rats [118]. The above data demonstrate possible protective roles of central α_{2A} antagonism in contrast to α_1 antagonism.

Peripheral adrenergic receptors mediate the effects of the sympathetic nervous system. Adrenergic and beta receptors seems to have both protective and harmful effects on metabolic regulation [119]. Sympathetic nervous system overreaction may be associated with AIMD [120] and have reciprocal connections with metabolic syndrome and obesity [121]. Central and peripheral D_2/α_2 antagonism could increase catecholamine release and sympathetic activity [122]. $\alpha_{1/2}$ antagonism by antipsychotics can compensate some of the effects of increased sympathetic tone [4, 43]. Beta receptor stimulation has divergent effects on energy balance and insulin sensitivity [123, 124]. Despite the possible protective effects of beta receptor signaling, sustained sympathetic hyperactivity seems to disrupt beta receptor density and function [121]. As a result, antipsychotics could indirectly influence β adrenergic signaling, given their low affinity to these receptors.

Hepatic insulin resistance and glucose output may be important pathogenetic steps of metabolic syndrome and AIMD [62, 101]. Hypothalamus could affect hepatic glucose and lipid metabolism through the autonomous nervous system. Central administration of olanzapine to mice activates hypothalamic AMPK and increases hepatic glucose production, probably mediated by sympathetic nervous system and beta-adrenergic signaling [125]. Adrenergic receptors may also regulate pancreatic, adipose and skeletal muscle metabolism. Rodent studies suggest that peripheral α_1 antagonism reduces peripheral vascular resistance, but it can also decrease insulin-independent glucose uptake by adipose tissue and skeletal muscles [119]. Conversely, α_2 antagonism may promote insulin sensitivity [52] and possibly regulate WAT lipolysis along with insulin and glucagon secretion [119].

3.6. NMDA and GABA_A Receptor

Glutamate receptors are possible targets of antipsychotic treatment and may play important roles in metabolic regulation [10, 126]. Clozapine and other antipsychotics, to a lesser degree, could act as weak agonists of NMDA receptors. NMDA receptors are activated when both glutamate and D-serine or D-glycine are binding to different sites of the receptor. Clozapine might activate the receptor by acting like D-serine [49, 127]. D-serine administration seems to suppress unhealthy feeding behaviors in mice [128]. Recently NMDA receptors were detected in mouse and human pancreatic islets. Their blockade could be therapeutic adjuvant for type 2

diabetes, by increasing insulin secretion and beta cell survival [129].

GABA_A receptors are structured by a configuration of α , β and γ subunits. Clozapine, olanzapine and maybe other antipsychotics could act as weak antagonists of GABA_A receptors [49, 130]. Administration of GABA_A antagonists to rats suppresses food intake by acting on energy balance centers [131]. Additionally, preclinical studies suggest that GABA_A receptors are also expressed in pancreatic islets, where their stimulation increases glucose-dependent insulin, decreases glucagon secretion and promotes cell survival [132].

3.7. Glucose Transporter Inhibition

Comparisons of central and peripheral administration of olanzapine to rats suggest that hyperglycemia and insulin resistance may be provoked in periphery. They also propose that the primary mediator could be the inhibition of glucose uptake in non-hepatic tissues [26]. Additionally, disrupted glucose-lipid utilization seems to precede insulin resistance in antipsychotic-treated rodents. Inhibition of multiple glu-

cose transporters could be a probable but unlikely mechanism [133, 134]. However, antipsychotic drugs may inhibit directly and/or indirectly glucose transportation in the CNS and periphery, but the exact mechanisms are unknown [13]. A possible mechanism is the interaction of antipsychotic drugs with conserved residues in glucose transporters, mainly the insulin-sensitive GLUT₄ [135]. Aerobic exercise and CB₁ antagonists seems to ameliorate olanzapine-induced metabolic side effects in rats, accompanied by increasing GLUT₄ in skeletal muscles and WAT [136, 137], suggesting the importance of glucose transporters in AIMD.

3.8. Drugs of Abuse, Opioid and Cannabinoid Receptors

Substance abuse is common in patients with schizophrenia, especially nicotine, cannabis, alcohol and psychostimulants [138]. Antipsychotic drugs could also predispose to substance abuse *per se*. Chronic and continuous administration of antipsychotics, especially typical, could upregulate D₂ receptors and increase reward-sensitivity to drugs [139]. Alcohol and drugs of abuse seems to predispose to metabolic syndrome and they are associated with eating disorders, malnutrition, neurotoxicity and hepatotoxicity [140]. As a

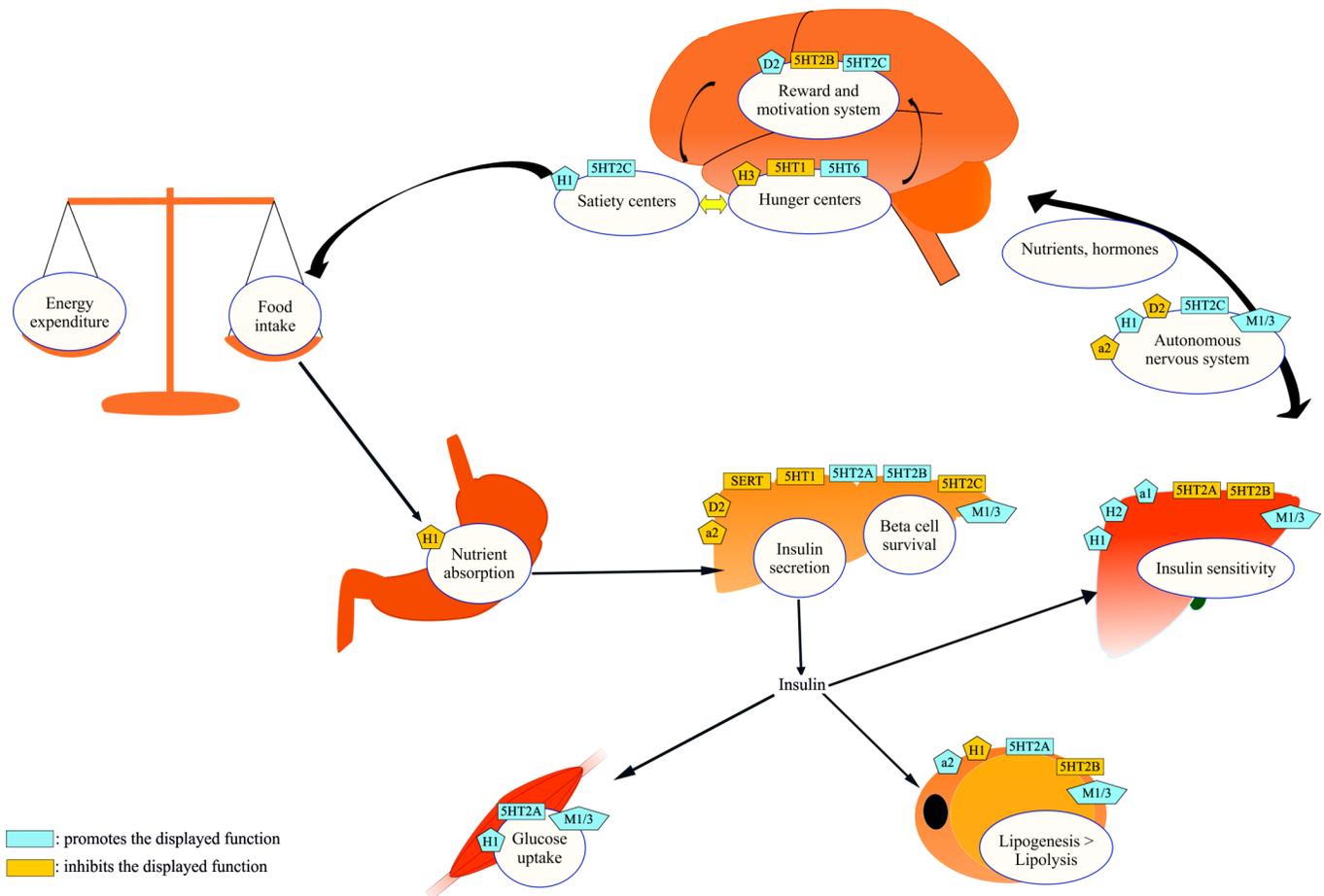


Fig. (1). Metabolic regulation and neurotransmitter receptors: the “canvas” of antipsychotic-induced metabolic dysfunctions. CNS and peripheral organs are the two major levels of metabolic regulation. They have bidirectional neuroendocrine connections and express neurotransmitter receptors. Energy balance (energy intake-energy expenditure), adipose tissue function, insulin secretion and insulin sensitivity are important sections of proper metabolic regulation. Antipsychotic drugs, by acting on neurotransmitter receptors, could alter this system and induce metabolic dysfunctions. (The color version of the figure is available in the electronic copy of the article).

result, comorbid substance abuse could worsen AIMD. Psychostimulants, such as amphetamine and cocaine, mainly target monoamine systems. They can alter metabolic regulation and they have been used as anorectic agents [64]. However, cocaine seems to increase palatable food intake without increasing weight in men, probably by increasing sympathetic activity and energy expenditure [141].

Opioid and cannabinoid receptors are widely expressed in energy balance and reward systems. Morphine, a μ opioid agonist, and THC or CB₁ agonists can increase food intake [64]. Clinical evidence suggests D₂ antagonism could interfere with opioid signaling in order to induce weight gain. According to that, naltrexone, a μ/κ opioid antagonist, was able to attenuate antipsychotic-induced weight gain in over-

Table 2. Association between pharmacological activity, central and peripheral levels of metabolic regulation.

	Effects	
	Central	Peripheral
D_{2/3} antagonism	↑ Food intake	↑ Insulin secretion
	↑ hypothalamic AMPK	↑ Proliferation and survival of beta cells
	↑ EPS	Deplete insulin stores (chronic)
	↑ Catecholamine release	
	↑ Prolactin	
5-HT₁ partial agonism	↓ Food intake	↓ Insulin secretion
	↓ EPS	↓ Glucose uptake (adipose tissue)
	↓ Prolactin	
5-HT_{2A} antagonism	↑ Food intake	↓ Insulin secretion
	↓ EPS	↑ Hepatic insulin sensitivity
	↓ Prolactin	↓ Glucose uptake (skeletal muscle)
		↓ Adipose tissue lipogenesis
5-HT_{2C} antagonism	↑ Food intake	↑ Insulin secretion(?)
	ANS disruption	
H₁ antagonism	↑ Food intake	↓ Hepatic insulin sensitivity
	↑ hypothalamic AMPK	↓ Glucose uptake (adipose tissue, skeletal muscle)
	↑ Sedation	↑ Adipose tissue lipogenesis
	ANS disruption	↑ Fructose absorption
		↑ Atherosclerosis
M₃ antagonism	↑ Food intake	↓ Insulin secretion
	↓ EPS	↓ Adipose tissue lipogenesis
	ANS disruption	↓ Glucose uptake (skeletal muscle)
alpha₁ antagonism	↑ Food intake	↓ Hepatic insulin sensitivity
	↑ hypothalamic AMPK	↓ Peripheral vascular resistance
	↑ Sedation	↓ Glucose uptake (adipose tissue, skeletal muscle)
	ANS disruption	
alpha₂ antagonism	↓ Food intake	↑ Insulin secretion
		↓ Adipose tissue lipogenesis
	↑ Catecholamine release	

Neurotransmitter receptors have both protective and harmful effects on metabolism. Secondary metabolic effects, e.g. by ANS disruption, are not mentioned.

weight women, possibly the portion mediated by D₂ antagonism [142]. Additionally, *in vivo* rodent studies propose the involvement of central and peripheral endocannabinoid signaling in AIMD. Both central and peripheral CB₁ antagonism could attenuate olanzapine-induced metabolic alterations in rats. However, CB₁ antagonists with low BBB permeability may affect preferentially the periphery and they could counteract AIMD without having the side effects of central CB₁ antagonism, such as suicidality and depression [137].

CONCLUSION

Antipsychotic-induced metabolic side effects are at the forefront of psychopharmacology, but their pathogenesis remains unknown. The current model consists of three inter-related but quite independent pathogenetic pathways: weight gain, insulin resistance and beta cell dysfunction [21]. These pathways are jointly regulated by the CNS, ANS and peripheral organs, where receptors are expressed (Fig. 1). Neurotransmitter receptors and transporters may mediate AIMD (Table 2), but the primary and secondary targets are unclear. Furthermore, there is evidence that antipsychotic drugs have negligible affinities to receptors involved in weight gain [143] and possibly insulin resistance and diabetes.

Actions in multiple brain regions, such as the hypothalamus, the reward system and the brainstem and in peripheral organs may disrupt food intake and metabolic regulation. The combination of 5-HT_{2C}/D₂/H₁ antagonism affects these regions and it is suggested to be the core mechanism of antipsychotic induced weight gain and diabetes [5, 54]. Antagonism of 5-HT_{2A}, 5-HT₆, M₃ and alpha₁ may have additive central and/or peripheral harmful effects, whereas of alpha_{2A} quite protective. Antipsychotics with lower metabolic risk seem to lack 5-HT_{2C} antagonism (amisulpride, haloperidol) or have additional protective mechanisms, such as D_{2/3} and/or 5-HT₁ partial agonism (aripiprazole, lurasidone, and ziprasidone). However, D_{2/3} or 5-HT₁ partial agonism may also disrupt beta cell function and insulin secretion [74, 90]. As a result, “metabolic neutral” drugs may also be capable of inducing metabolic side effects [91].

Antipsychotic drugs may also alter the expression of various receptors, neurotransmitter release along with brain structure and function. These adaptations in central and peripheral systems may mediate important indirect functions of antipsychotic drugs [42, 72]. In addition antipsychotic drugs seem to interfere with the immune system, gut microflora, hormone secretion, function and signaling [13, 144], with yet unclear mechanisms. These indirect mechanisms could help cover the translational gap from binding profiles to metabolic liabilities. As a result, the effects of antipsychotics on metabolism should be considered as the net result of direct receptor mechanisms combined with indirect and compensatory mechanisms, such as changes in receptor expression and neurotransmitter release. Moreover, AIMD exhibits quite distinct time-dependent stages [145], possibly mediated by different receptors and adaptive responses to antipsychotics.

Further preclinical and clinical research is needed in order to elucidate all the pathogenetic mechanisms. Moreover, theoretical and data-driven computational models could help

decipher the primary elements of binding profiles and the downstream pathways that mediate AIMD. Consequently, the translation of drug binding profiles to metabolic liability would be of great clinical importance, by guiding therapeutic decision making and intelligent drug design.

LIST OF ABBREVIATIONS

AgRP	=	Agouti-related peptide
AIMD	=	Antipsychotic-induced metabolic dysfunctions
AMPK	=	5' adenosine monophosphate-activated protein kinase
ANS	=	Autonomous nervous system
BBB	=	Blood brain barrier
CNS	=	Central nervous system
DVC	=	Dorsal vagal complex
EPS	=	Extrapyramidal symptoms
GLP-1	=	Glucagon-like peptide 1
GLUT	=	Glucose transporter
GPCR	=	G protein-coupled receptor
NPY	=	Neuropeptide Y
POMC	=	Pro-opiomelanocortin
SERT	=	Serotonin transporter
T2D	=	Type 2 diabetes mellitus
THC	=	Tetrahydrocannabinol

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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